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(54) Title: POLYMERIC DIFFUSION MATRIX CONTAINING 5-[(3,4-DIMETHOXYPHENETHYL)METHYLAMINO]-2-(3,4-DIMETHOXYPHENYL)-2-ISOPROPYLVALERONITRILE

(57) Abstract

A self-supporting polymeric diffusion matrix for the sustained release of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile in order to deliver the 5-[D(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to a patient and to provide the patient with an anti-anginal effect and with relief from other heart disorders. The matrix comprises from about 1 to about 60 % of a polar plasticizer, from about 6 to about 30 % by weight polyvinylalcohol, from about 2 to about 30 % by weight polyvinylpyrrolidone, and about 2 to 5 % of the 5-[(3,4-dimethoxyphenethyl)methylamino]D-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to provide a sustained release of said 5[(3,4-dimethoxyphenethyl)methylamino]BD-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile over a prolonged period.

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POLYMERIC DIFFUSION MATRIX CONTAINING 5-[(3,4-DIMETHOXYPHENETHYL)METHYLAMINO]-2-(3,4-DIMETHOXYPHENYL)-2-ISOPROPYLVALERONITRILE

The present invention relates to a polymeric diffusion matrix containing 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile, also known as Verapamil. More particularly, the invention relates to a polymeric diffusion matrix containing 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile characterized by a sustained release of the 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile. 5-[(3,4-Dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile is a well known drug which acts as a calcium permeability blocking agent and is employed against angina pectoris and other heart disorders which respond to calcium permeability blocking.

A self-supporting polymeric diffusion matrix is provided for the sustained release of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile in order to deliver said 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to a patient and provide said patient with an anti-angina effect, said matrix comprising from about 1 to about 60% by weight of a polar plasticizer; from about 6 to about 30% by weight polyvinylalcohol; form about 2 to about 30% by weight polyvinylpyrrolidone; and a pharmaceutically effective amount of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile about 2

to 5% by weight, to provide a sustained release of said 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile over a prolonged period.

Polar plasticizers suitable for use in this invention include principally poly-lower alkylene oxides, but other polar plasticizers such as diethylphthalic diethylphthalate may be used.

In one embodiment the polar plasticizer is glycerol present in an amount of from about 2 to about 60% by weight. In another embodiment the polar plasticizer is polyethylene glycol present in an amount of from about 1 to about 15% by weight. A still further embodiment contemplates a mixture of glycerol and polyethylene glycol wherein the latter is present in an amount by weight of from about 1 to about 5 parts per weight glycerol.

The self-supporting polymeric diffusion matrix generally contains a mixture of polyvinylalcohol and polyvinylpyrrolidone, although it will be understood that other polymeric mixtures may be used provided they yield the desired sustained release effect. For example, both the polyvinylalcohol and the polyvinylpyrrolidone may be partially or completely replaced with from about 1 to about 9% agar or agarose, and preferably from about 1.5 to 3% agar or agarose, 2% agar or agarose being particularly preferred.

As the polyvinylalcohol used in the present invention, there is generally contemplated one having a molecular weight from about 50,000 to about 150,000, and more preferably about 100,000 to about 150,000, 115,000 having been used in related systems of the inventors with success. The polyvinylalcohol should be hydrolyzed, generally at least to the extent of 90% with a preferred embodiment being at least 95% hydrolyzed. The polyvinylpyrrolidone should have a molecular weight of

from about 15,000 to about 85,000, and more preferably from about 20,000 to about 60,000. Polyvinylpyrrolidone with a molecular weight of 40,000 is particularly preferred.

The amount by weight of the ingredients other than the polar plasticizer generally should be in the following ranges: Polyvinylalcohol is generally present in an amount of from about 6 to about 30% by weight, with 20% being a preferred embodiment; polyvinylpyrrolidone is present generally in an amount of from about 2 to about 30% by weight, with about 10% being preferred.

In particular embodiments of this invention the total amount of polyvinylalcohol and polyvinylpyrrolidone used is from about 25 to about 50% by weight.

The water-soluble polymer can be replaced with (in addition to agar) gum arabic, gum tragacanth, polyacrylic acid, polymethacrylic acid, polyvinyloxazolidone, polyvinylmorpholinone, and polyvinylpiperidone.

Polyalkylene glycols (poly-lower alkylene oxides) such as polyethylene glycol and polypropylene glycol may replace all or part of the glycerol.

In forming the matrix, excess water is not required. In accordance with a preferred aspect of the invention, about 5% by weight 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile is included in the diffusion matrix. The resultant homogeneous mixture is poured into forms preferably made of glass or stainless steel. For transdermal application, a diffusion matrix with a thickness of about 1 to about 3 mm is in accordance with a preferred aspect of this invention. This diffusion matrix can be cut to obtain the desired surface area once it is suitably cured.

The following methods may be used for preparing the diffusion matrix of the invention.

In one method, the matrix is formed at atmospheric pressure. Water and polar plasticizer are first mixed together. A polar plasticizer such as glycerol or polyethylene glycerol is a necessary component in the matrix. A matrix formed without a polar plasticizer is not flexible and has poor diffusional contact with the skin, causing unreliable diffusion release. The polyvinylalcohol and polyvinylpyrrolidone are then added to the polar plasticizer water mixture at room temperature with agitation. The mixture is heated to a temperature within the range of from 90 to about 95°C at atmospheric pressure to extend the polymers. If desired, the mixture may be maintained at an elevated temperature for a period of time, based on polymer stability, prior to addition of the drug. Thus, the mixture is stable for a period of time and may be kept for such a period before being mixed with the drug to be delivered to the patient. Thereafter, the mixture is temperature-adjusted and the drug to be applied to the patient is then added to the mixture, with thorough agitation. Once a homogeneous mixture of the polymer solution and drug is obtained, the mixture is read to be cast to form in a drug-containing diffusion matrix. After casting, the mixture is cooled to a temperature such that gelation occurs.

In another method, the polymeric material is heated under pressure to accomplish dissolution in the mixture, the 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile is mixed in and the material is extruded under pressure into a mold of suitable size and geometry. The use of pressure allows for the incorporation of higher amounts of polymeric material into the matrix, up to 60% total polyvinylpyrrolidone and polyvinylalcohol content, thus improving film strength content, and dimensional stability and

allowing for thinner matrices. This pressure method further reduces or eliminates altogether curing and/or drying time.

It has been further found that curing is facilitated by subjecting the matrix to a temperature down to about -20°C immediately after casting, especially when polyethylene glycol is used as the plasticizer. The setting time is quickened considerably.

Sodium dodecyl sulfate or sorbitan (Tween-20) or other detergents may be added in an amount of 0.1 to 10% by weight, based on the matrix, as a dispersing agent, if desired. Soy phosphatides may be added as drug solubilizing agents in a concentration of 0.1-10% by weight. Up to 10% of one or more absorption facilitators to insure skin penetration such as dimethylsulfoxide, decylmethylsulfoxime, or other penetration enhancers may also be added. Suitable preservatives, such as sodium benzoate, may be also added where indicated.

The present drug delivery device comprises the drug-containing diffusion matrix which can be applied as a transdermal patch with means for fastening the matrix to the skin of a patient. Such means can take various forms, such as an occlusive backing layer forming a kind of "bandage" with the diffusion matrix being held against the skin of a patient being treated. A polyethylene or Mylar tape is contemplated as one form of occlusive layer in accordance with the invention. It can also take the form of an elastic band, such as a cloth band, a rubbery band or other material. Here, the diffusion matrix is placed directly on the skin and held in place over the arm or wrist of the patient. An intermediate adhesive layer between the diffusion matrix and the skin capable of permitting the transdermal application of the drug can also be used.

The invention is illustrated by the following non-limiting examples:

EXAMPLE I

Together there are mixed 20 gm glycerol and 55 ml water. This mixture is heated to 90°C; after reaching at least 70°C, there are slowly added 15 gm polyvinyl-alcohol (polyvinylalcohol 100% hydrolyzed, molecular weight 115,000) and 8 gm polyvinylpyrrolidone (m.w. 40,000). The mixture is stirred at 90°C until solution is effected, which may take about 10 minutes; it will be appreciated that with larger quantities, a considerably longer period of time may be needed. 98 ml of this solution is then mixed with 2 gm 5-[(3,4-dimethoxyphen-ethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropyl-valeronitrile, this mixture then being mechanically stirred until homogeneous. The homogeneous mixture is then poured into forms made of glass or stainless steel which serve as templates to produce a diffusion matrix having a thickness of about 0.2 to 2 mm. This diffusion matrix is then cut into square pieces of about 1 inch on each side, i.e., to provide a total surface of about 6.5 cm^2.

The diffusion matrix is applied to the skin of a patient in need of an anti-anginal effect, the 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile being transdermally delivered. The diffusion matrix is ideally applied to the skin of the patient by means of a single-piece bandage having the diffusion matrix in the center under the occlusive layer, the bandage being provided to the patient with a peel-of cover much like a "band-aid".

EXAMPLE II

In place of the glycerol of Example I, there is substituted 10 gm polyethylene glycol having a molecular

weight of 1000 and 10 ml water. The resultant diffusion matrix is more rigid than the of Example I.

EXAMPLE III

In place of the polyvinylalcohol and polyvinylpyrrolidone of Example I, there are substituted 2 gm agarose and 21 ml water, yielding a diffusion matrix for the delivery of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile.

EXAMPLE IV

The following mixture, listed in parts by weight, is heated under pressure, about 3 atmospheres being suitable, to 110-130°C:

Polyvinylalcohol	20 parts	(115,000 m.w.)
Polyvinylpyrrolidone	15 parts	(40,000 m.w.)
Polyethylene glycol	5 parts	(4,000 m.w.)
Glycerol	3 parts	
Verapamil	5 parts	
Water	to 100 parts	

This mixture is first prepared by heating polyvinylalcohol and water to effect dissolution. The polyethylene glycol molecular weight 4000, polyvinylpyrrolidone and glycerol are dissolved in cold water, and the two aqueous mixtures are brought together under heat and pressure as described above. Finely divided 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile is rapidly mixed into the viscous liquid and the mixture is extruded into an appropriate mold.

EXAMPLE V

In place of polyethylene glycol molecular weight 4000, of Example IV, polyethylene glycol molecular weight 1000 is used in the mixture.

WHAT IS CLAIMED IS

1. A self-supporting polymeric diffusion matrix for the sustained release of 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile in order to deliver said 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to a patient and provide said patient with an anti-anginal effect and relief from other heart disorders, said matrix comprising from about 1 to about 60% of a polar plasticizer, from about 6 to about 30% by weight polyvinylalcohol, from about 2 to about 30% by weight polyvinylpyrrolidone, and about 2 to 5% of the 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile to provide a sustained release of said 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile over a prolonged period.

2. The polymeric diffusion matrix of claim 1, wherein the total content of polyvinylalcohol and polyvinylpyrrolidone is from about 25% to about 60% by weight, based on the weight of the matrix.

3. The polymeric diffusion matrix of claim 1 or 2, wherein said polar plasticizer is glycerol.

4. The polymeric diffusion matrix of claim 3, wherein said polyvinylalcohol has a molecular weight of about 50,000 to about 150,000.

5. The polymeric diffusion matrix of claim 3, wherein said polyvinylalcohol has a molecular weight of about 100,000 to about 150,000.

6. The polymeric diffusion matrix of claim 3, wherein said polyvinylpyrrolidone has a molecular weight of from about 15,000 to about 85,000.

7. The polymeric diffusion matrix of claim 3, wherein said polyvinylpyrrolidone has a molecular weight of from about 20,000 to about 60,000.

8. The polymeric diffusion matrix of claim 1 or 2, wherein said polar plasticizer is polyethylene glycol present in an amount of about 1 to about 15% weight.

9. The polymeric diffusion matrix of claim 1 or 2, wherein said polar plasticizer is a mixture of glycerol and polyethylene glycol, wherein said polyethylene glycol is present in an amount by weight of from about 1 to 5 parts per weight glycerol.

10. The polymeric diffusion matrix of claim 1, wherein comprising about 20% by weight polyvinylalcohol of molecular weight about 115,000, about 15% by weight of polyvinylpyrrolidone of molecular weight about 40,000, about 5% by weight polyethylene glycol of molecular weight about 4000 and about 3% by weight glycerol.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US82/00925

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[3] A61L 15/03

U.S. Cl. 424/28; 424/78; 424/80

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/28, 424/78, 424/80

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

Chemical Abstracts

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
P	U.S., A, 4,291,015, Published 22 September 1981, KEITH et al	1 to 10
A	U.S., A, 4,210,633, Published 1 July 1980, TAKRURI et al	1 to 10
A	U.S., A, 3,742,951, Published 3 July 1973, ZAFFARONI	1 to 10
A	U.S., A, 3,287,222, Published 22 November 1966, LARDE et al	1 to 10
A	U.S., A, 2,693,438, Published 2 November 1954, WARD	1 to 10
A	U.S., A, 2,155,658, Published 25 April 1939, HORRMANN et al	1 to 10
A	U.S., A, 2,160,503, Published 30 May 1939, HORRMANN et al	1 to 10
A	GB, A, 493561, Published 11 October 1938, VOHRER	1 to 10

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
14 October 1982	19 OCT 1982
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Sharon K. Rice

Form PCT/ISA/210 (second sheet) (October 1981)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	Chemical Abstracts Volume 94, Issued 1981 (Columbus, Ohio, USA) see page 311 column 2 the ABSTRACT 94: 20412e, KEITH et al (KEY PHARMACEUTICALS, INC.) EUR. PAT. APPL. 13,606, 23 July 1980, "POLYMERIC DIFFUSION MATRIX AND DRUG DELIVERY DEVICE COMPRISING SAID MATRIX"	1 to 10
A	Chemical Abstracts Volume 86, Issued 1977 (Columbus, Ohio, USA) see page 380 columns 1 and 2 ABSTRACT 86: 161344f SASUKI et al JAPAN KOKAI 76,112,511, 26 March 1975, "CATHPLASM"	1 to 10

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, 16 with indication, where appropriate, of the relevant passages 17	Relevant to Claim No 18
A	Chemical Abstracts Volume 47, Issued 1953 (Columbus, Ohio, USA) see column 7165 DEI ITO et al BULL. PHARM. RESEARCH. INST. JAPAN. NO. 2: 1-12, "PHARMACEUTICAL STUDIES ON OINTMENTS AND EXTERNAL REMEDIES"	1 to 10
A	Chemical Abstracts Volume 92, Issued 1980 see page 350 column 2 ABSTRACT 92: 169275D, ANIKAWA et al JPN. KOKAI TOKKYO KOHO 79,151,115, 28 November 1979, "MEDICATED WET PACKS" (Columbus Ohio USA)	1 to 10
A	Chemical Abstracts Volume 89, Issued 1978 (Columbus Ohio USA) see page 548 column 1 ABSTRACT 89: 117911b, ARAI et al JAPAN KOKAI 78 50,320, 08 May 1978, "HYDROPHILIC PLASTERS"	1 to 10
A	Chemical Abstracts Volume 87, Issued 1977 (Columbus, Ohio, USA) see page 330 column 1 ABSTRACT 87: 141303j, TAURA et al, JAPAN KOKAI 77 38016, 24 March 1977, "POULTICES"	1 to 10